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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,337	01/16/2004	George Tidmarsh	544922000100	7716

20350 7590 05/09/2005

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EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,337	TIDMARSH, GEORGE	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1-20 ARE PRESENTED FOR EXAMINATION

Applicant's Information Disclosure Statement filed 11/3/2004 has been received and entered into the application. As reflected by the attached, completed form PTO/SB/08A (5 pages total), the Examiner has considered the cited references.

Claim Objection

In claim 19, "200 and 1000 mg" apparently should read as a range, rather than two separate dosage amounts. Appropriate correction is required.

Claim Rejection - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating benign prostatic hypertrophy ("BPH"), does not reasonably provide enablement for the prophylaxis or the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Burden on the Examiner for Making a Rejection Under 35 U.S.C. § 112 First Paragraph

As set forth in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971):

"[A] [s]pecification disclosure which contains teaching of manner and process of making and using the invention in terms corresponding to the scope to those used in

describing and defining subject matter sought to be patented must be taken as in compliance with enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contain therein which must be relied on for enabling support*; assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in specification is truly enabling." (emphasis added).

Here, the objective truth of the statement BPH can be prophylaxed, i.e., prevented, is doubted because given the state of the art as discussed below, it is believed that one skilled in the art would not readily accept or reasonably expect that BPH could actually be prevented. Absent such an expectation, the artisan would need to resort to undue experimentation in order to achieve the claimed objective of prophylaxis of BPH. The term "prophylaxis" is interpreted as meaning that BPH can be kept from *ever* occurring. It is noted that prophylaxis does not *necessarily* carry this meaning, however, it is within the scope of the term and thus meets the "broad and reasonable" standard as set forth in the MPEP at § 2111.

Also, the term "prophylaxis" is synonymous with the term "curing" and both circumscribe methods of absolute success. Because absolute success is not reasonably possible with most diseases/disorders, especially those having an etiology and pathophysiological manifestations as complex/poorly understood as BPH, (concerning the pathophysiological characteristics of BPH, Isaacs et al. (cited by the Examiner, abstract only), states that "several *theories* have been proposed to explain the etiology of the pathological phase of BPH" (middle of the abstract)), the expectation in the art would be that this disease/disorder could only be effectively treated. The specification contains no objective showing to the contrary of such an expectation and as such, is viewed as lacking an enabling disclosure of the same.

Respecting the pathology of BPH, the art was aware that this condition occurs in a vast majority of men and does not have a clearly defined point of origin. Thus, in *Harrison's Principles of Internal Medicine*, it is taught that "Development of prostatic hyperplasia is an almost universal phenomenon in aging men." (page 1862, col. 1, first sentence under the heading "Prostatic Hyperplasia"). Also, this reference teaches "The pathogenesis is not well understood..." (page 1862, col. 1, second paragraph under the heading "Pathogenesis"). In order to prevent a given disease/disorder, such would require that the preventative agent be administered before the appearance of the disease/disorder and be effective to keep the disease/disorder from ever occurring. That is, if the agent were administered after the disease/condition exists, prevention would not be possible because one cannot prevent something from occurring after it has occurred.

Here, the determination of exactly when BPH begins is uncertain and the present specification provides no teaching for making such a determination. Such a determination would be necessary to define a prophylactic administration from a therapeutic one. Further, Isaacs et al. (cited by the Examiner, abstract only) teach "The natural history of [BPH] involves two phases. The first, or pathological phase of BPH, involves two stages, termed microscopic and macroscopic BPH, neither of which produces symptomatic clinical dysuria."(first sentence of the abstract). A treatment for the symptoms of BPH would not be a prevention for BPH itself, because prostatic hyperplasia would more likely than not have already begun. Therefore, the Examiner doubts the objective truth of the statement in the specification that BPH may actually be prophylaxed.

Also, it is doubted that the symptoms may be kept from ever occurring. In support of this position, the Examiner relies on the following: "More recently, studies

have shown that medical treatment with 5 alpha-reductase inhibitors and possibly also alpha blockers may alter the natural history and progression of BPH" (Kirby, cited by the Examiner, abstract only, last sentence). Kirby does not indicate that the history and progression of BPH may be stopped or reversed, but rather only "altered" which would not imbue the skilled artisan with an expectation that the symptoms of the disease could be kept from ever occurring. *Principles of Internal Medicine* appears to support the Examiner's position because it is taught therein that even for effective treatments for BPH, the complete abolishment of symptoms does not occur. Thus, it is taught that "Both finasteride and alpha-adrenergic blockers produce *moderate and durable* improvements in symptoms in *some* patients and may be useful in symptomatic patients who do not wish to undergo surgery, *but the long-term effectiveness of medical therapy is not established.*" (page 1862, col. 2, first paragraph, last sentence under the heading "Treatment").

Thus, for the above reasons, the Examiner doubts the accuracy of the statement that the claimed active agent(s) may actually provide prophylaxis against BPH. Not possessing a reasonable expectation of success, it is further believed that the skilled artisan would be required to resort to undue experimentation in order to achieve this objective.

Accordingly, the claims are deemed properly rejected.

Overcoming This Rejection

In order to overcome the present rejection, Applicant may wish to consider replacing the concept of prophylaxis in the claims with reducing the symptoms of BPH as described in the present specification at page 4, paragraph [0017].

Claim Rejection - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention." (MPEP 2173).

The term "analog" in claims 1, 7, 16 and 17 is not defined by the claim or specification and thus there is no standard for ascertaining to what degree a given compound may be analogous to lonidamine and still be considered an analog as intended by Applicant. As defined by *Stedman's Medical Dictionary* (cited by the Examiner), the term "analog" merely means "A compound that resembles another in structure but is not necessarily an isomer" (page 65, col. 2). The definition does not point to any objective standard for assessing whether one compound "resembles" another.

Also, the term "about" in the expressions "greater than about 2 ng/ml" (claim 5), "less than about 10 ng/ml" (claim 6), "between about 1 mg and about 300 mg" (claim 11), "between about 300 mg and about 5 grams" (claim 12), "at least about 20%" (claim

15) and "about 1 mg to about 2000 mg" (claim 20) is a relative term which renders the claim indefinite. The expression "about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and thus one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Because the terms "analog" and "about" has not been defined in a clear, objective manner, such would require subjective interpretations of whether or not a particular compound or value is included by or excluded from the present claims.

It is therefore the Examiner's position that the public would not be informed of the boundaries of what constitutes infringement of the present claims and thus, the claims fail to meet either the tenor or express requirements of 35 U.S.C. § 112, second paragraph and are properly rejected.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Besner et al. (cited by Applicant, reference "10") who, at page 48, col. 2, under the heading "Source of Drug", teach lonidamine 300 mg. capsules and 50-, 150- and 300-mg scored tablets. Oral administration is indicated on page 48, line 2 of the abstract. The 50 mg. dosage form is in range of from 1 mg and 70 mg and thus anticipates such range.

The statement in the present claim that the composition is "for treatment of BPH" does not impart any physical or otherwise material characteristic to the claimed

composition that is not in the composition of the reference and thus does not serve as a patentable distinction.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (U.S. Patent No. 5,260,327, cited by Applicant, reference "3") in view of Hu et al. (U.S. Patent No. 6,482,802, cited by the Examiner) and Molnar-Kimber et al. (U.S. Patent No. 6,428,968, cited by the Examiner).

Kim et al. teach the oral administration of lonidamine "at from about 100 mg t.i.d. to about 200 mg t.i.d., and preferably at about 150 mg t.i.d. or at a dosage of about 25 mg/kg/day to about 200 mg/kg/day, preferably at 50 mg/kg/day" (col. 4, lines 56-61).

The differences between the above and the claimed subject matter lies in that Kim et al. fail to teach a "unit dose" and the specific dosage ranges claimed by Applicant and a "sustained release" dosage form (claim 20).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because Applicant's claimed dosage amounts represent dosages of between 1 mg and 70 mg, 200 mg and 1000 mg, and from about 1 mg to about 2000 mg (this being in a sustained dosage form) while the amounts in Kim et al. are as indicated

above which would have been expected to vary given the term "about" employed by the patentees and the fact that the dosage amounts expressed in "mg/kg/day" would depend on the weight of the patient being treated.

Also, the determination of the optimum dosage regimen to treat the disclosed conditions of Kim et al., i.e., brain and hepatic metastases (see the abstract) would have been a matter well within the purview of one of ordinary skill in the art and such determination would have been made in accordance with a variety of factors. These would have included the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered a part of a drug combination. Thus, the dosage regimen that would have actually been employed would have varied widely and, in the absence of evidence to the contrary, the currently claimed specific dosage amounts are not seen to be inconsistent the dosages that would have been determined by the skilled artisan.

Also, Kim et al. indicates that administration may be effected "continuously" which reasonably suggests that sustained or continuous dosage form should be employed. One of ordinary skill in the art would have been motivated to employ a sustained dosage for based not only on the express teaching by Kim et al., but also in order to facilitate the administration of the active agents in a convenient manner. Further, the art was aware of sustained release dosage forms which could contain lonidamine as the active agent for the purpose of, like Kim et al., treating brain or liver cancer (see Molnar-Kimber et al. at col. 4, lines 12, 34 and 38 and col. 12, lines 1-3).

Further, Molnar-Kimber et al. refer to unit dosages at col. 12, lines 4-9 and teach that the pharmaceutical compositions utilized by them may be prepared by "any method known or hereafter developed in the art of pharmacology...then, if necessary or desirable, shaping or packaging the product into a desired single- or muti-dose unit." (col. 11, lines 21-28). It is believed that such a disclosure would be seen as applicable to not only the active agents of Molnar-Kimber et al., but other active agents as well, including the actives of the primary reference. The skilled artisan would have been motivated to employ such technology because of the need to produce pharmaceutically acceptable dosage forms for use in accomplishing the desired therapeutic objective.

The combined teaching of the references relied on appear to establish that the claimed lonidamine pharmaceutical compositions would have been obvious and thus, the claims are deemed properly rejected.

The references cited on the attached form PTO-892 and not relied on are included to show the general state of the art.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

May 4, 2005